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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,596	12/05/2001	Colin Bernard Reese	P 0282829	7915

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EXAMINER	
YOUNG, JOSEPHINE	
ART UNIT	**PAPER NUMBER**
1623	8

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,596	REESE ET AL.	
	Examiner	Art Unit	
	Josephine Young	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☒ Claim(s) 7-8 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Acknowledgement is made of applicant's preliminary amendment filed August 30, 2001, wherein a paragraph was added to specifically indicate that the present application is a national phase filing of International Application No. PCT/GB00/00965.

Receipt is acknowledged of a claim to foreign priority under 35 U.S.C. 119(a)-(d). A copy of the certified copy of the priority document has been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)) and has been placed of record in the file.

Claim Objections

Claims 7-8 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 7-8 have not been further treated on the merits.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for processes for the preparation of 2'-derivatized pyrimidine nucleosides, does not reasonably provide enablement for processes for the preparation of other 2'-derivatized nucleosides wherein B is a base other than a pyrimidine, such as a purine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which base other than a pyrimidine would be able to chemically bond to the 2'-position to form a leaving group, as per claim 2, for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as only pyrimidine nucleosides were assessed, out of the numerous known bases.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while pyrimidines are known to form anhydro-nucleosides, no purines have been found to form anhydronucleosides. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compositions needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there are some working examples of processes for the preparation of 2'-derivatized pyrimidine nucleosides, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "protecting group" in claims 1-8 renders the claims in which it appears indefinite. In the absence of specific protecting groups or distinct language to describe the protecting groups or the chemical names of the protecting groups of this invention, the identity of said protecting group would be difficult to describe and the metes and bounds of said protecting group that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The term "base" in claims 1-2 renders the claims in which it appears indefinite. In the absence of the specific bases or distinct language to describe the bases or the chemical names of the bases of this invention, the identity of said base would be difficult to describe and the metes and bounds of said base that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The term "optionally substituted" in claims 1-8 renders the claims in which it appears indefinite. In the absence of the specific moieties intended to effectuate modification by substitution or attachment to the moiety claimed, the term "optionally substituted" renders the claims in which it appears indefinite in all occurrences wherein Applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties Applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

The term "substantially anhydrous conditions" in claims 1-8 is a relative term that renders the claims indefinite. The term "substantially anhydrous conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In all occurrences, phrases referencing the meaning of a variable as defined in some alternative, preceding location, such as "above," in claims 1-8, without distinct reference to the particular location of said meaning or definition, renders the claims in which said phrase(s) appear indefinite. The reference to some alternative location for a definition is superfluous if the definition or meaning is already set forth in a claim or said definition or meaning is clearly set forth in an independent claim from which a claim depends. In all occurrences and under these circumstances, the phrases should be deleted from the claims as superfluous.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over International Patent Publication No. WO 96/27606 to ISIS PHARMACEUTICALS, INC. (ISIS) in view of the

article McGEE et al., Nucleosides& Nucleotides, 1996, 15 (11&12), 1797-1803 (McGEE), both cited in the IDS submitted August 30, 2001.

Applicant claims processes for the preparation of 2'-O-substituted nucleosides, and in particular, 2'-O-substituted uridines, by reacting a tris-O-substituted aluminum with a 2'-leaving group, for example a nucleobase chemically bonded to the 2'-position.

ISIS teaches a process for the synthesis of 2'-O-substituted pyrimidines and oligomeric compounds therefrom. See Abstract. On page 9, line 35 to page 10, line 16, ISIS discloses the synthesis of 2'-O-substituted pyrimidines via a reaction of the corresponding 2-2'-anhydropyrimidine nucleoside with a Lewis acid. Further, on page 11, lines 12-18, ISIS teaches that the methodology can be used for the preparation of 2'-O-substituted uridines, which can be aminated to give a 2'-O-substituted cytidine. On page 33, lines 11-27 that the Lewis acid are preferably the di- or trivalent cations of di- and trivalent metals, including magnesium, calcium, aluminum, zinc, chromium, copper, boron, tin, mercury, iron, manganese, cadmium, gallium and barium, and their complexes, including alkoxides. ISIS further discloses on page 26, lines 3-5, the Lewis acid can be tri-alkyl borate. Procedure 3 of Example 20 (page 46) teaches a conversion using tri-alkyl borate with 100% yield and 97% purity.

ISIS does not explicitly state that the Lewis acid can be tris-O-substituted aluminum (i.e. $Al(OR)_3$) in particular, and only specifically uses tris-O-substituted boron (i.e. $B(OR)_3$).

McGEE teaches a process for the synthesis of 2'-O-substituted uridine via a reaction of the corresponding 2-2'-anhydrouridine with magnesium or calcium alkoxide. See Abstract.

It would have been obvious to one of ordinary skill in the art to use any one of the disclosed Lewis acids of ISIS for the conversion of a 2-2'-anhydropyrimidine nucleoside to a 2'-

O-substituted pyrimidine, including a tris-O-substituted aluminum (i.e. $Al(OR)_3$), as it is known in the art that several of the disclosed Lewis acids, namely magnesium and calcium alkoxide of McGEE, and tri-alkyl borate of ISIS, are effective such reaction. A skilled artisan would have been motivated and would have had a reasonable expectation of success to use a Lewis acid of equivalent or comparable activity to convert the 2-2'-anhydropyrimidine nucleoside to a 2'-O-substituted pyrimidine.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-8 are pending. Claims 1-6 are rejected. Claims 7-8 are objected to and have not been further treated on the merits. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
May 14, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600